Search Strategy

FILE 'USPATFULL' ENTERED AT 22:37:57 ON 23 JUN 2003

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                E OLSON W C/IN
                E OLSON WILLIAM C/IN
L1           12 S E3
                E MADDON PAUL J/IN
L2           31 S E3
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FILE 'MEDLINE' ENTERED AT 22:47:42 ON 23 JUN 2003

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                E OLSON W C/AU
L3           24 S E3 OR E4
                E TILLEY S A/AU
L4           36 S E2 OR E3
L5           16 S L4 AND (CCR5 OR HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
                E DRAGIC T/AU
L6           27 S E3 OR E4
L7           21 S L6 NOT (L3 OR L4)
                E WILD C T/AU
L8            7 S E3-E5
                E WILD C P/AU
                E JIANG S/AU
L9          342 S E3
L10          48 S L9 AND PY=1999
                E ECKERT D M/AU
L11           5 S E3
                E NUNBERG J H/AU
L12          34 S E3
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FILE 'MEDLINE' ENTERED AT 23:27:40 ON 23 JUN 2003

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L13        2291 S CCR5
L14         456 S L13 AND ANTIBOD?
L15           2 S L14 AND (ANTI-CCR5 MABS)
L16         356 S L14 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L17         195 S L16 AND (INHIBIT? OR PREVENT?)
L18         108 S L17 AND (FUSION OR ENTRY)
                E FURUTA R A/AU
L19          10 S E3
L20      131782 S (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L21       19436 S L20 AND (ANTIBOD?)
L22           3 S L21 AND (FUSION INTERMEDIATE?)
L23         930 S L21 AND GP41
L24          23 S L23 AND (INTERMEDIATE OR CONFORMAT?-DEPENDENT)
L25        4164 S L21 AND (CD4)
L26        1243 S L25 AND GP120
L27         668 S L26 AND (INHIBIT? OR NEUTRALIZE? OR PREVENT?)
L28          52 S L27 AND (ANTI-CD4 MAB? OR ANTI-CD4 MONOCLONAL)
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FILE 'USPATFULL' ENTERED AT 00:15:17 ON 24 JUN 2003

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L29         661 S (CCR5)
L30         567 S L29 AND ANTIBOD?
L31         160 S L30 AND (ANTI-CCR5 MONOCLONAL OR ANTI-CCR5 MAB? OR ANTI-CCR5
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L32          152 S L31 AND ANTIBOD?/CLM
L33        24988 S (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L34        17525 S L33 AND ANTIBOD?
L35           15 S L34 AND (FUSION INTERMEDIATE?)
L36         1262 S L34 AND GP41
L37          128 S L36 AND (ANTI-GP41)
L38          116 S L37 AND (INHIBIT? OR NEUTRALIZE?)
L39           91 S L38 AND CD4
L40           22 S L39 AND (RECEPTOR BINDING OR CELL BINDING)

     FILE 'WPIDS' ENTERED AT 00:19:28 ON 24 JUN 2003

                E OLSON W C/IN
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L1 ANSWER 10 OF 12 USPATFULL
2002:24365 Method for preventing HIV-1 infection of CD4+ cells.
Allaway, Graham P., Mohegan Lake, NY, United States
Litwin, Virginia M., Fayetteville, NY, United States
Maddon, Paul J., Elmsford, NY, United States
Olson, William C., Ossining, NY, United States
Progenics Pharmaceuticals, Inc., Tarrytown, NY, United States (U.S. corporation)
US 6344545 B1 20020205
APPLICATION: US 1997-831823 19970402 (8)
PRIORITY: US 1996-19715P 19960614 (60)
US 1996-14532P 19960402 (60)
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention provides methods for inhibiting fusion of HIV-1 to CD4.sup.+ cells which comprise contacting CD.sup.4+ cells with a non-chemokine agent capable of binding to a chemokine receptor in an amount and under conditions such that fusion of HIV-1 to the CD4.sup.+ cells is inhibited. This invention also provides methods for inhibiting HIV-1 infection of CD4.sup.+ cells which comprise contacting CD4.sup.+ cells with a non-chemokine agent capable of binding to a chemokine receptor in an amount and under conditions such that fusion of HIV-1 to the CD4.sup.+ cells is inhibited, thereby inhibiting the HIV-1 infection. This invention provides non-chemokine agents capable of binding to the chemokine receptor and inhibiting fusion of HIV-1 to CD4.sup.+ cells. This invention also provides pharmaceutical compositions comprising an amount of the non-chemokine agent capable of binding to the chemokine receptor and inhibiting fusion of HIV-1 to CD4.sup.+ cells effective to prevent fusion of HIV-1 to CD4.sup.+ cells and a pharmaceutically acceptable carrier.

CLM What is claimed is:
1. A method of inhibiting HIV-1 infection of a CD4+ cell which comprises contacting the CD4+ cell with an **antibody** or portion of an antibody capable of binding to a **chemokine receptor** on the surface of the CD4+ cell in an amount and under conditions such that **fusion** of **HIV-1** or an HIV-1 infected cell to the CD4+ cell is **inhibited**, thereby inhibiting HIV-1 infection of the CD4+ cell.

2. The method of claim 1, wherein the chemokine receptor is a **CCR5** chemokine receptor.

3. The method of claim 1, wherein the CD4+ cell is a PM-1 cell.

4. The method of claim 1, wherein the CD4+ cell is a primary CD4+ T-cell.

5. The method of claim 1, wherein the CD4+ cell is a PMBC cell.

6. The method of claim 1, wherein the antibody is a monoclonal antibody.

L3 ANSWER 14 OF 24 MEDLINE
96323171 Document Number: 96323171. PubMed ID: 8709277. Human immunodeficiency virus type 1 membrane fusion mediated by a laboratory-adapted strain and a primary isolate analyzed by resonance energy transfer. Litwin V; Nagashima K A; Ryder A M; Chang C H; Carver J M; Olson W C; Alizon M; Hasel K W; Maddon P J; Allaway G P. (Progenics Pharmaceuticals, Inc., Tarrytown, New York 10591, USA.) JOURNAL OF VIROLOGY, (1996 Sep) 70 (9) 6437-41. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Previous studies of human immunodeficiency virus type 1 (HIV-1) envelope glycoprotein-mediated membrane fusion have focused on laboratory-adapted T-lymphotropic strains of the virus. The goal of this study was to characterize membrane fusion mediated by a primary HIV-1 isolate in comparison with a laboratory-adapted strain. To this end, a new fusion assay was developed on the basis of the principle of resonance energy transfer, using HeLa cells stably transfected with gp120/gp41 from the T-lymphotropic isolate HIV-1LA1 or the macrophage-tropic primary isolate HIV-1JR-FL. These cells fused with CD4+ target cell lines with a tropism mirroring that of infection by the two viruses. Of particular note, HeLa cells expressing HIV-1JR-FL gp120/gp41 fused only with PM1 cells, a clonal derivative of HUT 78, and not with other T-cell or macrophage cell lines. These results demonstrate that the envelope glycoproteins of these strains play a major role in mediating viral tropism. Despite significant differences exhibited by HIV-1JR-FL and HIV-1LAI in terms of tropism and sensitivity to neutralization by CD4-based proteins, the present study found that membrane fusion mediated by the envelope glycoproteins of these viruses had remarkably similar properties. In particular, the degree and kinetics of membrane fusion were similar, fusion occurred at neutral pH and was dependent on the presence of divalent cations. Inhibition of HIV-1JR-FL envelope glycoprotein-mediated membrane fusion by soluble CD4 and CD4-IgG2 occurred at concentrations similar to those required to neutralize this virus. Interestingly, higher concentrations of these agents were required to inhibit HIV-1LAI envelope glycoprotein-mediated membrane fusion, in contrast to the greater sensitivity of HIV-1LAI virions to neutralization by soluble CD4 and CD4-IgG2. This finding suggests that the mechanisms of fusion inhibition and neutralization of HIV-1 are distinct.

L3 ANSWER 11 OF 24 MEDLINE
1998184599 Document Number: 98184599. PubMed ID: 9525686. CD4-immunoglobulin G2 protects Hu-PBL-SCID mice against challenge by primary human immunodeficiency virus type 1 isolates. Gauduin M C; Allaway G P; Olson W C; Weir R; Maddon P J; Koup R A. (The Aaron Diamond AIDS Research Center and The Rockefeller University, New York, New York 10016, USA.) JOURNAL OF VIROLOGY, (1998 Apr) 72 (4) 3475-8. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB CD4-immunoglobulin G2 (IgG2) is a fusion protein comprising human IgG2 in which the Fv portions of both heavy and light chains have been replaced by the V1 and V2 domains of human CD4. Previous studies found that CD4-IgG2 potently neutralizes a broad range of primary human immunodeficiency virus type 1 (HIV-1) isolates in vitro and ex vivo. The current report demonstrates that CD4-IgG2 protects against infection by primary isolates of HIV-1 in vivo, using the hu-PBL-SCID mouse model. Passive administration of 10 mg of CD4-IgG2 per kg of body weight protected all animals against subsequent challenge with 10 mouse infectious doses of the laboratory-adapted T-cell-tropic isolate HIV-1(LAI), while 50 mg of CD4-IgG2 per kg protected four of five mice against the primary isolates

HIV-1(JR-CSF) and HIV-1(AD6). In contrast, a polyclonal HIV-1 Ig fraction exhibited partial protection against HIV-1(LAI) at 150 mg/kg but no significant protection against the primary HIV-1 isolates. The results demonstrate that CD4-IgG2 effectively neutralizes primary HIV-1 isolates in vivo and can prevent the initiation of infection by these viruses.

L3 ANSWER 9 OF 24 MEDLINE
1999214354 Document Number: 99214354. PubMed ID: 10196311. Differential inhibition of human immunodeficiency virus type 1 fusion, gp120 binding, and CC-chemokine activity by monoclonal antibodies to CCR5. Olson W C; Rabut G E; Nagashima K A; Tran D N; Anselma D J; Monard S P; Segal J P; Thompson D A; Kajumo F; Guo Y; Moore J P; Maddon P J; Dragic T. (Progenics Pharmaceuticals, Inc., Tarrytown, New York 10591, USA.) JOURNAL OF VIROLOGY, (1999 May) 73 (5) 4145-55. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB The CC-chemokine receptor CCR5 mediates fusion and entry of the most commonly transmitted human immunodeficiency virus type 1 (HIV-1) strains. We have isolated six new anti-CCR5 murine monoclonal antibodies (MAbs), designated PA8, PA9, PA10, PA11, PA12, and PA14. A panel of CCR5 alanine point mutants was used to map the epitopes of these MAbs and the previously described MAb 2D7 to specific amino acid residues in the N terminus and/or second extracellular loop regions of CCR5. This structural information was correlated with the MAbs' abilities to inhibit (i) HIV-1 entry, (ii) HIV-1 envelope glycoprotein-mediated membrane fusion, (iii) gp120 binding to CCR5, and (iv) CC-chemokine activity. Surprisingly, there was no correlation between the ability of a MAb to inhibit HIV-1 fusion-entry and its ability to inhibit either the binding of a gp120-soluble CD4 complex to CCR5 or CC-chemokine activity. MAbs PA9 to PA12, whose epitopes include residues in the CCR5 N terminus, strongly inhibited gp120 binding but only moderately inhibited HIV-1 fusion and entry and had no effect on RANTES-induced calcium mobilization. MAbs PA14 and 2D7, the most potent inhibitors of HIV-1 entry and fusion, were less effective at inhibiting gp120 binding and were variably potent at inhibiting RANTES-induced signaling. With respect to inhibiting HIV-1 entry and fusion, PA12 but not PA14 was potently synergistic when used in combination with 2D7, RANTES, and CD4-immunoglobulin G2, which inhibits HIV-1 attachment. The data support a model wherein HIV-1 entry occurs in three stages: receptor (CD4) binding, coreceptor (CCR5) binding, and coreceptor-mediated membrane fusion. The antibodies described will be useful for further dissecting these events.

L3 ANSWER 6 OF 24 MEDLINE
2000413756 Document Number: 20341767. PubMed ID: 10882617. Single-dose safety, pharmacology, and antiviral activity of the human immunodeficiency virus (HIV) type 1 entry inhibitor PRO 542 in HIV-infected adults. Jacobson J M; Lowy I; Fletcher C V; O'Neill T J; Tran D N; Ketas T J; Trkola A; Klotman M E; Maddon P J; Olson W C; Israel R J. (Mount Sinai Medical Center, New York, NY 10029-6574, USA.. jeffrey.jacobson@mssm.edu) . JOURNAL OF INFECTIOUS DISEASES, (2000 Jul) 182 (1) 326-9. Journal code: 0413675. ISSN: 0022-1899. Pub. country: United States. Language: English.

AB PRO 542 (CD4-IgG2) is a recombinant antibody-like fusion protein wherein the Fv portions of both the heavy and light chains of human IgG2 have been replaced with the D1D2 domains of human CD4. Unlike monovalent and divalent CD4-based proteins, tetravalent PRO 542 potently neutralizes diverse primary human immunodeficiency virus (HIV) type 1 isolates. In this phase 1 study, the first evaluation of this compound in humans, HIV-infected adults were treated with a single intravenous infusion of PRO 542 at doses of 0.2-10 mg/kg. PRO 542 was well tolerated, and no

dose-limiting toxicities were identified. Area under the concentration-time curve, and peak serum concentrations increased linearly with dose, and a terminal serum half-life of 3-4 days was observed. No patient developed antibodies to PRO 542. Preliminary evidence of antiviral activity was observed as reductions in both plasma HIV RNA and plasma viremia. Sustained antiviral effects may be achieved with repeat dosing with PRO 542.

L3 ANSWER 4 OF 24 MEDLINE
2001092646 Document Number: 20578192. PubMed ID: 11134270. Potent, broad-spectrum inhibition of human immunodeficiency virus type 1 by the CCR5 monoclonal antibody PRO 140. Trkola A; Ketas T J; Nagashima K A; Zhao L; Cilliers T; Morris L; Moore J P; Maddon P J; Olson W C. (The Aaron Diamond AIDS Research Center, New York, USA.) JOURNAL OF VIROLOGY, (2001 Jan) 75 (2) 579-88. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB CCR5 serves as a requisite fusion coreceptor for clinically relevant strains of human immunodeficiency virus type 1 (HIV-1) and provides a promising target for antiviral therapy. However, no study to date has examined whether monoclonal antibodies, small molecules, or other nonchemokine agents possess broad-spectrum activity against the major genetic subtypes of HIV-1. PRO 140 (PA14) is an anti-CCR5 monoclonal antibody that potently inhibits HIV-1 entry at concentrations that do not affect CCR5's chemokine receptor activity. In this study, PRO 140 was tested against a panel of primary HIV-1 isolates selected for their genotypic and geographic diversity. In quantitative assays of viral infectivity, PRO 140 was compared with RANTES, a natural CCR5 ligand that can inhibit HIV-1 entry by receptor downregulation as well as receptor blockade. Despite their divergent mechanisms of action and binding epitopes on CCR5, low nanomolar concentrations of both PRO 140 and RANTES inhibited infection of primary peripheral blood mononuclear cells (PBMC) by all CCR5-using (R5) viruses tested. This is consistent with there being a highly restricted pattern of CCR5 usage by R5 viruses. In addition, a panel of 25 subtype C South African R5 viruses were broadly inhibited by PRO 140, RANTES, and TAK-779, although approximately 30-fold-higher concentrations of the last compound were required. Interestingly, significant inhibition of a dualtropic subtype C virus was also observed. Whereas PRO 140 potently inhibited HIV-1 replication in both PBMC and primary macrophages, RANTES exhibited limited antiviral activity in macrophage cultures. Thus CCR5-targeting agents such as PRO 140 can demonstrate potent and genetic-subtype-independent anti-HIV-1 activity.

L3 ANSWER 3 OF 24 MEDLINE
2001246662 Document Number: 21136452. PubMed ID: 11237840. Human immunodeficiency virus type 1 entry inhibitors PRO 542 and T-20 are potently synergistic in blocking virus-cell and cell-cell fusion. Nagashima K A; Thompson D A; Rosenfield S I; Maddon P J; Dragic T; Olson W C. (Progenics Pharmaceuticals, Tarrytown, New York 10591, USA.) JOURNAL OF INFECTIOUS DISEASES, (2001 Apr 1) 183 (7) 1121-5. Journal code: 0413675. ISSN: 0022-1899. Pub. country: United States. Language: English.

AB Human immunodeficiency virus type 1 (HIV-1) entry proceeds via a cascade of events that afford promising targets for therapy. PRO 542 neutralizes HIV-1 by blocking its attachment to CD4 cells, and T-20 blocks gp41-mediated fusion. Both drugs have shown promise in phase 1/2 clinical trials. Here, the drugs were tested individually and in combination in preclinical models of HIV-1 infection, and inhibition data were analyzed for cooperativity by using the combination index method. Synergistic

inhibition of virus-cell and cell-cell fusion was observed for phenotypically diverse viruses for a broad range of drug concentrations, often resulting in > or = 10-fold dose reductions in vitro. Additional mechanism-of-action studies probed the molecular basis of the synergies. The markedly enhanced activity observed for the PRO 542:T-20 combination indicates that the multistep nature of HIV-1 entry leaves the virus particularly vulnerable to combinations of entry inhibitors. These findings provide a strong rationale for evaluating combinations of these promising agents for therapy in vivo.

L5 ANSWER 14 OF 16 MEDLINE
92287631 Document Number: 92287631. PubMed ID: 1376135. Synergistic neutralization of HIV-1 by human monoclonal antibodies against the V3 loop and the CD4-binding site of gp120. Tilley S A; Honnen W J; Racho M E; Chou T C; Pinter A. (Public Health Research Institute, New York, NY 10016.) AIDS RESEARCH AND HUMAN RETROVIRUSES, (1992 Apr) 8 (4) 461-7. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

AB Two distinct regions or epitope clusters of human immunodeficiency virus type 1 (HIV-1) gp120 have been shown to elicit neutralizing antibodies: the V3 loop and the CD4-binding site. We have isolated neutralizing human monoclonal antibodies (HuMAbs) against conserved epitopes in both of these regions. In this study, we demonstrate that an equimolar mixture of two of these HuMAbs, one directed against the V3 loop and the other against the CD4-binding site, neutralizes HIV-1 at much lower concentrations than does either of the individual HuMAbs. Mathematical analysis of this effect suggests cooperative neutralization of HIV-1 by the two HuMAbs and demonstrates a high level of synergy, with combination indices (CIs) of 0.07 and 0.16 for 90% neutralization of the MN and SF-2 strains, respectively. The dose reduction indices (DRIs) for each of the two HuMAbs at 99% neutralization range approximately from 10 to 150. A possible mechanism for this synergism is suggested by binding studies with recombinant gp160 of the MN strain; these show enhanced binding of the anti-CD4 binding site HuMAb in the presence of the anti-V3 loop HuMAb. These results demonstrate the advantage of including both V3 loop and CD4-binding site epitopes in a vaccine against HIV-1 and indicate that combinations of HuMAbs against these two sites may be particularly effective in passive immunotherapy against the virus.

L5 ANSWER 15 OF 16 MEDLINE
92179521 Document Number: 92179521. PubMed ID: 1724568. A human monoclonal antibody against the CD4-binding site of HIV1 gp120 exhibits potent, broadly neutralizing activity. Tilley S A; Honnen W J; Racho M E; Hilgartner M; Pinter A. (Public Health Research Institute, New York, NY 10016.) RESEARCH IN VIROLOGY, (1991 Jul-Aug) 142 (4) 247-59. Journal code: 8907469. ISSN: 0923-2516. Pub. country: France. Language: English.

AB A human monoclonal antibody (HuMAb) against HIV1, 1125H, was isolated from an asymptomatic, seropositive haemophiliac. This antibody was specific for gp120, and its binding to gp120 was inhibited by soluble CD4, indicating that its epitope was in or near the CD4-binding site. 1125H antibody recognized a variety of divergent HIV1 strains, including most laboratory strains tested as well as some early passage isolates. Commensurate with its specificity and high apparent affinity, 1125H exhibited potent neutralizing activity against IIIB, MN, RF and SF-2 strains. The epitope recognized by 1125H was destroyed by reduction of disulphide bonds, but not by removal of N-linked sugars. Thus, the epitope was conformationally determined and did not involve carbohydrate.

Data from radioimmunoprecipitation/SDS-PAGE analysis of proteolytically cleaved viral lysate further indicated that the epitope of 1125H was not affected by cleavage at the V3 loop of gp120, provided that gp120 disulphide bonds remained intact. The potential use of HuMAb 1125H in passive immunotherapy against HIV is discussed as well as the importance of including its epitope in an AIDS vaccine.

L7 ANSWER 13 OF 21 MEDLINE
97433411 Document Number: 97433411. PubMed ID: 9287172. Co-receptors for HIV-1 entry. Moore J P; Trkola A; Dragic T. (The Aaron Diamond AIDS Research Center, The Rockefeller University, 455 First Avenue, New York, NY 10021, USA.. jmoore@adarc.org) . CURRENT OPINION IN IMMUNOLOGY, (1997 Aug) 9 (4) 551-62. Ref: 93. Journal code: 8900118. ISSN: 0952-7915. Pub. country: ENGLAND: United Kingdom. Language: English.

AB HIV-1 enters its target cells by fusion at the plasma membrane. The primary cellular receptor for HIV is CD4, but this molecule is insufficient to permit viral fusion. During 1996, the necessary entry co-factors (co-receptors or second receptors) were identified as being members of the seven-transmembrane-spanning receptor family fusin: CXCR4 for T-tropic strains and CCR5, principally, for M-tropic strains. The co-receptor functions of these proteins are inhibited by their natural alpha- and beta-chemokine ligands.

L8 ANSWER 5 OF 7 MEDLINE
1998206292 Document Number: 98206292. PubMed ID: 9546217. Capture of an early fusion-active conformation of HIV-1 gp41. Furuta R A; Wild C T; Weng Y; Weiss C D. (Office of Vaccines, Center for Biologics Evaluation and Research, Food and Drug Administration, Bethesda, Maryland 20892-4555, USA.) NATURE STRUCTURAL BIOLOGY, (1998 Apr) 5 (4) 276-9. Journal code: 9421566. ISSN: 1072-8368. Pub. country: United States. Language: English.

AB Using an inhibitory synthetic peptide (DP-178) from HIV-1 gp41, we have trapped HIV-1 envelope glycoprotein (Env) undergoing conformational changes during virus entry. Our data show that DP-178 binds gp41 and inhibits Env-mediated membrane fusion after gp120 interacts with cellular receptors, indicating that conformational changes involving the coiled coil domain of gp41 are required for entry. Capture of this fusion-active conformation of Env provides insights into the early events leading to Env-mediated membrane fusion.

L8 ANSWER 7 OF 7 MEDLINE
95024042 Document Number: 95024042. PubMed ID: 7937889. Peptides corresponding to a predictive alpha-helical domain of human immunodeficiency virus type 1 gp41 are potent inhibitors of virus infection. Wild C T; Shugars D C; Greenwell T K; McDanal C B; Matthews T J. (Department of Surgery, Duke University Medical Center, Durham, NC 27710.) PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1994 Oct 11) 91 (21) 9770-4. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB To define the role of the human immunodeficiency virus type 1 (HIV-1) envelope proteins in virus infection, a series of peptides were synthesized based on various regions of the HIV-1 transmembrane protein gp41. One of these peptides, DP-178, corresponding to a region predictive of alpha-helical secondary structure (residues 643-678 of the HIV-1LAI isolate), has been identified as a potent antiviral agent. This peptide consistently blocked 100% of virus-mediated cell-cell fusion at < 5 ng/ml (IC90 approximately 1.5 ng/ml) and gave an approximately 10 times reduction in infectious titer of cell-free virus at approximately 80

ng/ml. The inhibitory activity was observed at peptide concentrations approximately 10(4) to 10(5) times lower than those at which cytotoxicity and cytostasis were detected. Peptide-mediated inhibition is HIV-1 specific in that approximately 10(2) to 10(3) times more peptide was required for inhibition of a human immunodeficiency virus type 2 isolate. Further experiments showed that DP-178 exhibited antiviral activity against both prototypic and primary HIV-1 isolates. As shown by PCR analysis of newly synthesized proviral DNA, DP-178 blocks an early step in the virus life cycle prior to reverse transcription. Finally, we discuss possible mechanisms by which DP-178 may exert its inhibitory activity.

L11 ANSWER 1 OF 5 MEDLINE
2002061307 Document Number: 21645560. PubMed ID: 11395423. Mechanisms of viral membrane fusion and its inhibition. Eckert D M; Kim P S. (Howard Hughes Medical Institute, Whitehead Institute for Biomedical Research, Department of Biology, M.I.T., Cambridge, Massachusetts 02142, USA.. Eckert@wi.mit.edu) . ANNUAL REVIEW OF BIOCHEMISTRY, (2001) 70 777-810. Ref: 197. Journal code: 2985150R. ISSN: 0066-4154. Pub. country: United States. Language: English.

AB Viral envelope glycoproteins promote viral infection by mediating the fusion of the viral membrane with the host-cell membrane. Structural and biochemical studies of two viral glycoproteins, influenza hemagglutinin and HIV-1 envelope protein, have led to a common model for viral entry. The fusion mechanism involves a transient conformational species that can be targeted by therapeutic strategies. This mechanism of infectivity is likely utilized by a wide variety of enveloped viruses for which similar therapeutic interventions should be possible.

L12 ANSWER 4 OF 34 MEDLINE
2000209687 Document Number: 20209687. PubMed ID: 10742693. Turning a corner on HIV neutralization?. Nunberg J H; Follis K E; Trahey M; LaCasse R A. (Montana Biotechnology Center, The University of Montana, Missoula, MT 59812, USA.) Microbes Infect, (2000 Feb) 2 (2) 213-21. Ref: 90. Journal code: 100883508. ISSN: 1286-4579. Pub. country: France. Language: English.

AB HIV vaccine development has been hampered by the inability of conventional immunogens to elicit antibodies capable of neutralizing primary isolates of the virus. Recent studies using 'fusion-competent' immunogens that capture transitional intermediate structures of the functioning envelope protein suggest that this goal may now be achievable.

L12 ANSWER 5 OF 34 MEDLINE
1999105987 Document Number: 99105987. PubMed ID: 9888845. Fusion-competent vaccines: broad neutralization of primary isolates of HIV. LaCasse R A; Follis K E; Trahey M; Scarborough J D; Littman D R; Nunberg J H. (The Montana Biotechnology Center and Division of Biological Sciences, University of Montana, Missoula, MT 59812, USA.) SCIENCE, (1999 Jan 15) 283 (5400) 357-62. Journal code: 0404511. ISSN: 0036-8075. Pub. country: United States. Language: English.

AB Current recombinant human immunodeficiency virus (HIV) gp120 protein vaccine candidates are unable to elicit antibodies capable of neutralizing infectivity of primary isolates from patients. Here, "fusion-competent" HIV vaccine immunogens were generated that capture the transient envelope-CD4-coreceptor structures that arise during HIV binding and fusion. In a transgenic mouse immunization model, these formaldehyde-fixed whole-cell vaccines elicited antibodies capable of neutralizing infectivity of 23 of 24 primary HIV isolates from diverse geographic locations and genetic clades A to E. Development of these

fusion-dependent immunogens may lead to a broadly effective HIV vaccine.

L18 ANSWER 102 OF 108 MEDLINE
97404394 Document Number: 97404394. PubMed ID: 9256481. Antibodies to several conformation-dependent epitopes of gp120/gp41 inhibit CCR-5-dependent cell-to-cell fusion mediated by the native envelope glycoprotein of a primary macrophage-tropic HIV-1 isolate. Verrier F C; Charneau P; Altmeyer R; Laurent S; Borman A M; Girard M. (Departement de Virologie Moleculaire, Institut Pasteur, Paris, France.) PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1997 Aug 19) 94 (17) 9326-31. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB The beta-chemokine receptor CCR-5 is essential for the efficient entry of primary macrophage-tropic HIV-1 isolates into CD4(+) target cells. To study CCR-5-dependent cell-to-cell fusion , we have developed an assay system based on the infection of CD4(+) CCR-5(+) HeLa cells with a Semliki Forest virus recombinant expressing the gp120/gp41 envelope (Env) from a primary clade B HIV-1 isolate (BX08), or from a laboratory T cell line-adapted strain (LAI). In this system, gp120/gp41 of the "nonsyncytium-inducing," primary, macrophage-tropic HIV-1BX08 isolate, was at least as fusogenic as that of the "syncytium-inducing" HIV-1LAI strain. BX08 Env-mediated fusion was inhibited by the beta-chemokines RANTES (regulated upon activation, normal T cell expressed and secreted) and macrophage inflammatory proteins 1beta (MIP-1beta) and by antibodies to CD4, whereas LAI Env-mediated fusion was insensitive to these beta-chemokines. In contrast soluble CD4 significantly reduced LAI, but not BX08 Env-mediated fusion, suggesting that the primary isolate Env glycoprotein has a reduced affinity for CD4. The domains in gp120/gp41 involved in the interaction with the CD4 and CCR-5 molecules were probed using monoclonal antibodies. For the antibodies tested here, the greatest inhibition of fusion was observed with those directed to conformation-dependent, rather than linear epitopes. Efficient inhibition of fusion was not restricted to epitopes in any one domain of gp120/gp41. The assay was sufficiently sensitive to distinguish between antibody- and beta-chemokine-mediated fusion inhibition using serum samples from patient BX08, suggesting that the system may be useful for screening human sera for the presence of biologically significant antibodies.

L18 ANSWER 75 OF 108 MEDLINE
1999194814 Document Number: 99194814. PubMed ID: 10092648. Epitope mapping of CCR5 reveals multiple conformational states and distinct but overlapping structures involved in chemokine and coreceptor function. Lee B; Sharron M; Blanpain C; Doranz B J; Vakili J; Setoh P; Berg E; Liu G; Guy H R; Durell S R; Parmentier M; Chang C N; Price K; Tsang M; Doms R W. (Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, Pennsylvania 19104, USA.) JOURNAL OF BIOLOGICAL CHEMISTRY, (1999 Apr 2) 274 (14) 9617-26. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB The chemokine receptor CCR5 is the major coreceptor for R5 human immunodeficiency virus type-1 strains. We mapped the epitope specificities of 18 CCR5 monoclonal antibodies (mAbs) to identify domains of CCR5 required for chemokine binding, gp120 binding, and for inducing conformational

changes in Env that lead to membrane fusion. We identified mAbs that bound to N-terminal epitopes, extracellular loop 2 (ECL2) epitopes, and multidomain (MD) epitopes composed of more than one single extracellular domain. N-terminal mAbs recognized specific residues that span the first 13 amino acids of CCR5, while nearly all ECL2 mAbs recognized residues Tyr-184 to Phe-189. In addition, all MD epitopes involved ECL2, including at least residues Lys-171 and Glu-172. We found that ECL2-specific mAbs were more efficient than NH2- or MD-antibodies in blocking RANTES or MIP-1beta binding. By contrast, N-terminal mAbs blocked gp120-CCR5 binding more effectively than ECL2 mAbs. Surprisingly, ECL2 mAbs were more potent inhibitors of viral infection than N-terminal mAbs. Thus, the ability to block virus infection did not correlate with the ability to block gp120 binding. Together, these results imply that chemokines and Env bind to distinct but overlapping sites in CCR5, and suggest that the N-terminal domain of CCR5 is more important for gp120 binding while the extracellular loops are more important for inducing conformational changes in Env that lead to membrane fusion and virus infection. Measurements of individual antibody affinities coupled with kinetic analysis of equilibrium binding states also suggested that there are multiple conformational states of CCR5. A previously described mAb, 2D7, was unique in its ability to effectively block both chemokine and Env binding as well as coreceptor activity. 2D7 bound to a unique antigenic determinant in the first half of ECL2 and recognized a far greater proportion of cell surface CCR5 molecules than the other mAbs examined. Thus, the epitope recognized by 2D7 may represent a particularly attractive target for CCR5 antagonists.

L22 ANSWER 2 OF 3 MEDLINE
2002321295 Document Number: 22045656. PubMed ID: 12050391. Dissection of human immunodeficiency virus type 1 entry with neutralizing antibodies to gp41 fusion intermediates. Golding Hana; Zaitseva Marina; de Rosny Eve; King Lisa R; Manischewitz Jody; Sidorov Igor; Gorny Miroslaw K; Zolla-Pazner Susan; Dimitrov Dimiter S; Weiss Carol D. (Division of Viral Products, Center for Biologics Evaluation and Research, Food and Drug Administration, Bldg. 29A Room 1A21, 8800 Rockville Pike, Bethesda, MD 20892, USA.. goldingh@cber.fda.gov) . JOURNAL OF VIROLOGY, (2002 Jul) 76 (13) 6780-90. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Human immunodeficiency virus type 1 (HIV-1) entry requires conformational changes in the transmembrane subunit (gp41) of the envelope glycoprotein (Env) involving transient fusion intermediates that contain exposed coiled-coil (prehairpin) and six-helix bundle structures. We investigated the HIV-1 entry mechanism and the potential of antibodies targeting fusion intermediates to block Env-mediated membrane fusion. Suboptimal temperature (31.5 degrees C) was used to prolong fusion intermediates as monitored by confocal microscopy. After transfer to 37 degrees C, these fusion intermediates progressed to syncytium formation with enhanced kinetics compared with effector-target (E/T) cell mixtures that were incubated only at 37 degrees C. gp41 peptides DP-178, DP-107, and IQN17 blocked fusion more efficiently (5- to 10-fold-lower 50% inhibitory dose values) when added to E/T cells at the suboptimal temperature prior to transfer to 37 degrees C. Rabbit antibodies against peptides modeling the N-heptad repeat or the six-helix bundle of gp41 blocked fusion and viral infection at 37 degrees C only if preincubated with E/T cells at the suboptimal temperature. Similar fusion inhibition was observed with human six-helix bundle-specific monoclonal

antibodies. Our data demonstrate that antibodies targeting gp41 fusion intermediates are able to bind to gp41 and arrest fusion. They also indicate that six-helix bundles can form prior to fusion and that the lag time before fusion occurs may include the time needed to accumulate preformed six-helix bundles at the fusion site.

L24 ANSWER 12 OF 23 MEDLINE
1999030935 Document Number: 99030935. PubMed ID: 9811763. A conformation-specific monoclonal antibody reacting with fusion-active gp41 from the human immunodeficiency virus type 1 envelope glycoprotein.
Jiang S; Lin K; Lu M. (Lindsley F. Kimball Research Institute, New York Blood Center, New York, New York 10021, USA.. sjiang@nybc.org) . JOURNAL OF VIROLOGY, (1998 Dec) 72 (12) 10213-7. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB The gp41 subunit of the human immunodeficiency virus type 1 (HIV-1) envelope glycoprotein plays a major role in the membrane fusion step of viral infection. The ectodomain of gp41 contains a six-helix structural domain that likely represents the core of the fusion-active conformation of the molecule. A **monoclonal antibody (MAb)**, designated **NC-1**, was generated and cloned from a mouse immunized with the model polypeptide N36(L6)C34, which folds into a stable six-helix bundle. NC-1 binds specifically to both the alpha-helical core domain and the oligomeric forms of **gp41**. This conformation-dependent reactivity is dramatically reduced by point mutations within the N-terminal coiled-coil region of gp41 which impede formation of the gp41 core. **NC-1 binds to the surfaces of HIV-1-infected cells only in the presence of soluble CD4**. These results indicate that **NC-1 is capable of reacting with fusion-active gp41 in a conformation-specific manner** and can be used as a valuable biological reagent for studying the receptor-induced conformational changes in gp41 required for membrane fusion and HIV-1 infection.

L28 ANSWER 13 OF 52 MEDLINE
1998001346 Document Number: 98001346. PubMed ID: 9343181. Neutralizing antibodies against the V3 loop of human immunodeficiency virus type 1 gp120 block the CD4-dependent and -independent binding of virus to cells.
Valenzuela A; Blanco J; Krust B; Franco R; Hovanessian A G. (Unite de Virologie et d'Immunologie Cellulaire, Institut Pasteur, Paris, France.) JOURNAL OF VIROLOGY, (1997 Nov) 71 (11) 8289-98. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB The CD4 molecule is an essential receptor for human immunodeficiency virus type 1 (HIV-1) through high-affinity interactions with the viral external envelope glycoprotein gp120. Previously, **neutralizing monoclonal antibodies (MAbs) specific to the third hypervariable domain of gp120** (the V3 loop) have been thought to block HIV infection without affecting the binding of HIV particles to CD4 -expressing human cells. However, here we demonstrate that this conclusion was not correct and was due to the use of soluble gp120 instead of HIV particles. Indeed, **neutralizing anti-V3 loop MAbs inhibited completely the binding** and entry **of HIV particles into CD4+ human cells**. In contrast, the binding of virus was only partially inhibited by neutralizing anti -CD4 MAbs against the gp120 binding site in

CD4, which, like the anti-V3 loop MAbs, completely inhibited HIV entry and infection. Nonneutralizing control MAbs against either the V3 loop or the N or C terminus of gp120 had no significant effect on HIV binding and entry. HIV-1 particles were also found to bind human and murine cells expressing or not expressing the human CD4 molecule. Interestingly, the binding of HIV to CD4+ murine cells was inhibited by both anti-V3 and anti-CD4 MAbs, whereas the binding to human and murine CD4- cells was affected only by anti-V3 loop MAbs. The effect of anti-V3 loop neutralizing MAbs on the HIV binding to cells appears not to be the direct consequence of gp120 shedding from HIV particles or of a decreased affinity of CD4 or gp120 for binding to its surface counterpart. Taken together, our results suggest the existence of CD4-dependent and -independent binding events involved in the attachment of HIV particles to cells; in both of these events, the V3 loop plays a critical role. As murine cells lack the specific cofactor CXCR4 for HIV-1 entry, other cell surface molecules besides CD4 might be implicated in stable binding of HIV particles to cells.

L41 ANSWER 15 OF 21 WPIDS (C) 2003 THOMSON DERWENT
AN 2000-431480 [37] WPIDS
DNC C2000-131148
TI Preventing and treating human immunodeficiency virus (HIV) infections using compounds that inhibit interactions between HIV and its fusion co-receptor, especially antibodies specific for the CCR5 chemokine receptor.
DC B04 D16
IN MADDON, P J; OLSON, W C
PA (PROG-N) PROGENICS PHARM INC
CYC 29
PI WO 2000035409 A2 20000622 (200037)* EN 68p
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: AU CA JP MX
AU 2000021996 A 20000703 (200046)
EP 1144006 A2 20011017 (200169) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
JP 2002538771 W 20021119 (200281) 65p
ADT WO 2000035409 A2 WO 1999-US30345 19991216; AU 2000021996 A AU 2000-21996 19991216; EP 1144006 A2 EP 1999-966466 19991216, WO 1999-US30345 19991216; JP 2002538771 W WO 1999-US30345 19991216, JP 2000-587730 19991216
FDT AU 2000021996 A Based on WO 200035409; EP 1144006 A2 Based on WO 200035409; JP 2002538771 W Based on WO 200035409
PRAI US 1998-212793 19981216; US 1998-112532P 19981216

AB WO 200035409 A UPAB: 20000807
NOVELTY - A composition (I) for inhibiting human immunodeficiency virus (HIV)-1 infection, comprising at least 2 synergistic compounds (especially antibodies specific for chemokine receptor CCR5) for inhibiting HIV infection, is new. At least 1 of the compounds prevents productive interaction between HIV-1 and a HIV-1 fusion co-receptor.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a method (II) for treating a subject infected with HIV-1, or preventing a subject becoming infected, comprising administering (I);

(2) an anti-CCR5 monoclonal antibody (III), selected from PA8 (ATCC HB-12605), PA9 (ATCC HB-12606), PA10 (ATCC HB-12607), PA11 (ATCC HB-12608), PA12 (ATCC HB-12609) and/or PA14 (ATCC HB-12610);

(3) a nucleic acid molecule (IV) encoding the light chain from (III);

(4) a nucleic acid molecule (V) encoding the heavy chain from (III);

(5) a nucleic acid molecule (VI) encoding the Fab chain from (III);

(6) a nucleic acid molecule (VII) encoding the CDR (complementary determining region) from (VIII); and

(7) nucleic acid molecules (IX) encoding the variable region from (III).

ACTIVITY - Viricidal.

MECHANISM OF ACTION - Inhibition of interactions between HIV-1 and HIV-1 fusion co-receptors, especially antibody inhibition of CCR5 chemokine receptor binding.

HIV-1 envelope-mediated fusion between HeLa-EnvJR-FL+ and PM1 cells was detected using the RET (resonance energy transfer) assay. Equal numbers (2 multiply 104) of fluorescein octadecyl ester (F18)-labeled envelope expressing cells and octadecyl rhodamine (R18)-labeled PM1 cells were plated in 96-well plates in 15% fetal calf serum in DPBS (undefined) and incubated for 4 hours (h) at 37 deg. C in the presence of varying concentrations of the anti-CCR5 mAbs (monoclonal antibodies), PA8 to PA12, PA14, 2D7 or a non-specific murine IgG1. Fluorescence RET was measured with a Cytofluor (RTM) plate-reader and % RET was determined as described by Litwin V et al., HIV-1 membrane fusion mediated by laboratory adapted

strain and a primary isolate analyzed by resonance energy transfer, J. Virol., 70:6437-6441.

NLluc+env- viruses complemented in trans by envelope glycoproteins from JR-FL or Gun-1 were produced as previously described by Dragic TV et al., Amino terminal substitutions in the CCR5 co-receptor impair gp120 binding and HIV-1 entry, J. Virol., 72:279-285. U87MG-CD4+CCR5+ cells were infected with chimeric, reporter viruses containing 50-100 ng/ml p24 in the presence of varying concentrations of the individual mAbs. After 2h at 37 deg. C, virus-containing media were replaced by fresh, mAb-containing media. Fresh media, without antibodies, was added again after 12 h. After a total of 72h, 100 microliters of lysis buffer were added to the cells and luciferase activity (r.l.u.) was measured as described by Dragic et al., supra. The percentage inhibition of HIV-1 infection was defined as (1-(r.l.u in the presence of antibody / r.l.u in the absence of antibody)) x 100%.

All 6 mAbs and mAb 2D7 blocked fusion between CD4+CCR5+ PM1 cells and HeLa-EnvJR-FL+ cells in the RET assay. The descending rank order of potency was 2D7, PA14, PA12, PA11, PA10, PA9, PA8. The IC50 values for PA14 and 2D7 were 1.7 micrograms/ml and 1.6 micrograms/ml (respectively), for PA11 and PA12 is was 25.5 micrograms/ml and 10 micrograms/ml (respectively). PA8, PA9 and PA10 inhibited fusion by 10-15% at 300 micrograms/ml. None of the mAbs affected fusion between PM1 cells and HeLa-EnvLai+ cells which express the full length envelope protein from an X4 virus.

USE - (I) is used for preventing and treating infections caused by HIV-1 viruses (e.g. acquired immunodeficiency syndrome (AIDS)).
Dwg.0/6

L41 ANSWER 12 OF 21 WPIDS (C) 2003 THOMSON DERWENT
AN 2001-483270 [52] WPIDS
CR 2002-362300 [39]
DNC C2001-144961
TI Composition for inhibiting Human Immunodeficiency Virus (HIV)-1 infection in CD4+ cells, comprising a mixture of compounds that retard HIV-1 attachment to CD4+ cells and a compound that retards gp41 mediating fusion of HIV-1 to CD4+ cells.
DC B04 D16
IN MADDON, P J; OLSON, W C
PA (PROG-N) PROGENICS PHARM INC; (MADD-I) MADDON P J; (OLSO-I) OLSON W C
CYC 95
PI WO 2001055439 A1 20010802 (200152)* EN 61p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
AU 2001031184 A 20010807 (200174)
EP 1252325 A1 20021030 (200279) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
US 2003082185 A1 20030501 (200331)
ADT WO 2001055439 A1 WO 2001-US2633 20010126; AU 2001031184 A AU 2001-31184 20010126; EP 1252325 A1 EP 2001-903356 20010126, WO 2001-US2633 20010126; US 2003082185 A1 US 2000-493346 20000128
FDT AU 2001031184 A Based on WO 200155439; EP 1252325 A1 Based on WO 200155439
PRAI US 2000-493346 20000128

AB WO 200155439 A UPAB: 20030516
NOVELTY - A composition (C) comprises a mixture of 2 compounds (relative mass ratio in the range of 100:1-1:100), one of which (C1) retards

attachment of Human Immunodeficiency Virus (HIV)-1 to a CD4+ cell, and the other compound (C2) retards gp41 from adopting a conformation capable of mediating fusion of HIV-1 to a CD4+ cell, and which inhibits HIV-1 infection of the CD4+ cell, is new.

DETAILED DESCRIPTION - A composition (C) comprises a mixture of 2 compounds (relative mass ratio in the range of 100:1-1:100), one of which (C1) retards attachment of Human Immunodeficiency Virus (HIV)-1 to a CD4+ cell, and the other compound (C2) retards gp41 from adopting a conformation capable of mediating fusion of HIV-1 to a CD4+ cell, and which inhibits HIV-1 infection of the CD4+ cell, is new.

C1 retards attachment of HIV-1 to a CD4+ cell by retarding binding of HIV-1 gp120 envelope glycoprotein to CD4 on the surface of the CD4+ cell. C2 retards gp41 from adopting a conformation capable of mediating fusion of HIV-1 to a CD4+ cell by non-covalently binding to an group on a gp41 fusion intermediate.

ACTIVITY - Virucidal; anti-HIV.

MECHANISM OF ACTION - Inhibitor of HIV-1 infection of CD4+ cell (claimed).

HIV-1 envelope-mediated fusion between HeLa-EnvJR-FL and PM1 cells was detected using a Resonance Energy Transfer (RET) assay. Equal numbers (2 multiply 104) of fluorescein octadecyl ester (F18)-labeled envelope-expressing cells and octadecyl rhodamine (R18)-labeled PM1 cells were plated in 96-well plates in 15% fetal calf serum in phosphate buffered saline and incubated for 4 hours at 37 deg. C in the presence of varying concentrations of CD4-IgG2 and/or T-20.

Fluorescence RET was measured with a Cytofluor (RTM) plate-reader and percent RET was determined. Combinations of inhibitors of HIV-1 attachment and gp41 fusion intermediates were first tested for the ability to inhibit HIV-1 env-mediated membrane fusion in the RET assay.

This assay was proved to be a highly successful model of the HIV-1 entry process. The fusion assay and infectious virus were similarly sensitive to inhibition by metal chelators and agents that target the full complement of viral and cellular receptors.

USE - (C) is useful for inhibiting HIV-1 infection of a CD4+ cell, by contacting the CD4+ cell with (C) (claimed).

Dwg.0/3

L41 ANSWER 5 OF 21 WPIDS (C) 2003 THOMSON DERWENT
AN 2003-237965 [23] WPIDS
DNC C2003-060885
TI Reducing HIV infected subject's HIV-1 viral load, by administering antibody which binds to CCR5 chemokine receptor and inhibits fusion of HIV-1 to CD4+CCR5+ cell.
DC B04 D16 P83
IN MADDON, P J; OLSON, W C
PA (MADD-I) MADDON P J; (OLSO-I) OLSON W C; (PROG-N) PROGENICS PHARM INC
CYC 100
PI US 2002146415 A1 20021010 (200323)* 47p
WO 2002083172 A1 20021024 (200323) EN
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG UZ VN YU ZA ZM ZW
ADT US 2002146415 A1 US 2001-828615 20010406; WO 2002083172 A1 WO 2002-US10752 20020405
PRAI US 2001-828615 20010406

AB US2002146415 A UPAB: 20030407
NOVELTY - Reducing an HIV infected subject's HIV-1 viral load, comprises

administering to the subject a viral load reducing amount of an antibody which binds to CCR5 chemokine receptor, and inhibits fusion of HIV-1 to a CD4+CCR5+ cell, so as to reduce the subject's HIV-1 viral load to 50% or less of the subject's HIV-1 viral load prior to administering the antibody to the subject.

ACTIVITY - Anti-HIV. PRO 140 (PA14) an anti-CCR5 monoclonal antibody that potentially inhibits HIV-1 entry at concentrations that does not affect CCR5's chemokine receptor activity. PRO 140 (PA14) was examined for activity in a therapeutic animal model of HIV-1 infection. SCID mice were reconstituted with normal human peripheral blood mononuclear cells and infected 2 weeks later with HIV-1(JR-CSF), a primary CCR5-using virus. When viral steady state was reached (approximately 8-10 days post infection), animals were treated intraperitoneally with a single 1 mg dose of PA14 or control antibody. Plasma viral loads were monitored pre and post-injection by reverse transcription-PCR (RT-PCR) Amplicor Assay, an assay for measuring the amount of HIV RNA in a subject's plasma by reverse transcribing and amplifying the HIV RNA prior to quantifying the RNA. The RNA was quantified by hybridization with a labeled probe. Viral loads decreased to undetectable levels in each of PA14-treated animals and remained undetectable for 6-9 days post-injection, whereas viral loads remained steady in control animals. In these studies, single dose PA14 demonstrated potent antiviral activity in the hu-PBL-SCID mouse model of HIV infection. It was expected that not only multi-dose PA14 but also PA14 when used in combination with other HIV-1 entry inhibitors inhibited HIV infection in humans.

MECHANISM OF ACTION - Inhibitor of fusion of HIV-1 to CD4+CCR5+ cell.

USE - The method is useful for reducing an HIV infected subject's HIV-1 viral load to 33% or 10% or less of the subject's HIV-1 viral load prior to administering the antibody to the subject. The subject is in particular a human being (claimed). The method is useful for treating a subject who has become afflicted with HIV.

Dwg.0/13

L41 ANSWER 4 OF 21 WPIDS (C) 2003 THOMSON DERWENT
AN 2003-238109 [23] WPIDS
CR 1999-080861 [07]; 2000-571320 [53]; 2002-215082 [27]
DNC C2003-060929
TI Inhibiting fusion of human immunodeficiency virus-1 to CD4+ cells for treating HIV-1 infection, by contacting CD4+ cells with a non-chemokine agent capable of binding to a chemokine receptor.
DC A96 B04 D16
IN ALLAWAY, G P; LITWIN, V M; MADDON, P J; OLSON, W C
PA (PROG-N) PROGENICS PHARM INC
CYC 1
PI US 2002155429 A1 20021024 (200323)* 23p
ADT US 2002155429 A1 Provisional US 1996-14532P 19960402, Provisional US 1996-19715P 19960614, Cont of US 1997-831823 19970402, US 2001-888938 20010625
PRAI US 2001-888938 20010625; US 1996-14532P 19960402; US 1996-19715P 19960614; US 1997-831823 19970402

AB US2002155429 A UPAB: 20030407
NOVELTY - Inhibiting (M1) fusion of human immunodeficiency virus-1 (HIV-1) to CD4+ cells comprising contacting CD4+ cells with a non-chemokine agent capable of binding to a chemokine receptor in an amount and under conditions such that fusion of HIV-1 to the CD4+ cells is inhibited, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a non-chemokine agent (I) capable of binding to a chemokine receptor and inhibiting fusion of HIV-1 to CD4+ cells;

(2) an agent (II) capable of binding to CXCR4 and inhibiting HIV-1 infection;

(3) a composition of matter (III) capable of binding to a chemokine receptor and inhibiting fusion of HIV-1 to CD4+ cells, comprising a non-chemokine agent linked to a ligand capable of binding to a cell surface receptor of the CD4+ cells other than the chemokine receptor such that the binding of the non-chemokine agent to the chemokine receptor does not inhibit the binding of the ligand to the other receptor;

(4) a composition of matter (IV) capable of binding to the chemokine receptor and inhibiting fusion of HIV-1 to CD4+ cells, comprising a non-chemokine agent linked to a compound capable of increasing the in vivo half-life of the non-chemokine agent;

(5) a pharmaceutical composition (V) comprising (I), (II), (III) or (IV), to inhibit fusion of HIV-1 to CD4+ cells; and

(6) determining (M2) whether a non-chemokine agent is capable of inhibiting the fusion of HIV-1 to CD4+ cell, by:

(a) contacting:

(i) a CD4+cell which is labeled with a first dye; with

(ii) a cell expressing the HIV-1 envelope glycoprotein on its surface, which is labeled with a second dye, in the presence of excess of the agent under conditions permitting the fusion of the CD4+ cell to the cell expressing the HIV-1 envelope glycoprotein on its surface in the absence of the agent, the first and second dyes being selected so as to allow resonance energy transfer between the dyes;

(b) exposing the product to conditions which result in resonance energy transfer if fusion has occurred; and

(c) determining whether there is a reduction of resonance energy transfer, when compared with the resonance energy transfer in the absence of the agent, a decrease in transfer indicating that the agent is capable of inhibiting the fusion of HIV-1 to CD4+ cells.

ACTIVITY - Anti-HIV.

MECHANISM OF ACTION - Bind to chemokine receptors and inhibit fusion of HIV-1 to CD4+.

Replication of primary, non-syncytium-inducing (NSI) human immunodeficiency virus-1 (HIV-1) isolates in CD4+ T cells was inhibited by the C-C beta -chemokines MIP-1 alpha , MIP-1 beta , RANTES (1,2), but T-cell line-adapted (TCLA) or syncytium-inducing (SI) primary strains were insensitive. To study how beta -chemokines inhibited HIV-1 replication, a virus entry assay based on single-cycle infection by an env-deficient virus, NL4/3 Delta env complemented by envelope glycoproteins expressed in trans was used. Various env-complemented viruses were tested in PM1 cells, a variant of HUT-78 that had the unique ability to support replication of primary and TCLA HIV-1 strains, allowing comparison of envelope glycoprotein functioned against a common cellular background. MIP-1 alpha , MIP-1 beta and RANTES were most active against HIV-1 in combination and strongly inhibited infection of PM1 cells by complemented viruses whose envelopes were derived from NSI primary ADA and BaL. PM1 cells were cultured. CD4+ lymphocytes were maintained in culture medium containing interleukin-2. Target cells (1-2 multiply 105) were infected with supernatants (10-50 ng of HIV-1 p24) from 293-cells co-transfected with an NL4/3 Delta env-luciferase vector and a HIV-1 env-expressing vector. beta -chemokines were added to the target cells simultaneously with virus. After 2 hours, the cells were washed twice with phosphate buffered saline (PBS), resuspended in beta -chemokine-containing media and maintained for 48-96 h. Luciferase activity in cell lysates was measured. RANTES and MIP-1 beta were strongly active when added individually, while other beta -chemokines-MIP-1 alpha , MCP-1, MCP-2 and MCP-3 were weaker inhibitors. However, MIP-1 alpha , MIP-1 beta and RANTES, in combination, did not inhibit infection of PM1 cells by TCLA strains NL4/3 and HxB2, or by the amphotropic murine leukemia virus (MuLV-Ampho) pseudotype. The env-complementation assay was used to assess HIV-1 entry into CD4+ T-cells

from two control individuals. MIP-1 alpha , MIP-1 beta and RANTES strongly inhibited infection by the NSI primary strain JR-FL infection of LW4's and LW5's CD4+ T-cells, and weakly reduced HxB2 infection of LW cells. It was determined when beta -chemokines inhibited HIV-1 replication by showing that complete inhibition of infection of PM1 cells required the continuous presence of beta -chemokines for 5 hours after addition of ADA or BaL env-complemented virus.

USE - (M1) is useful for inhibiting fusion of HIV-1 to CD4+ cells, for inhibiting HIV-1 infection of CD4+ cells. (V) is useful for reducing the likelihood of HIV-1 infection and for treating HIV-1 infection in a subject (claimed).

Dwg.0/5